Mucosal vaccines based on the use of cholera toxin B subunit as immunogen and antigen carrier.

Lebens M, Holmgren J

Department of Medical Microbiology and Immunology, University of Goteborg, Sweden.

Stimulation of strong mucosal IgA immune responses as a basis for vaccine-induced protection against various pathogens has proved difficult. Most soluble protein antigens administered either parenterally or oral-mucosally have given disappointing results. A notable exception in this regard are cholera toxin (CT) and, particularly in humans, its non-toxic B subunit pentamer moiety (CTB) both of which stimulate a strong intestinal IgA antibody response and long-lasting immunological memory. Based on this, CTB has become an important component in recently developed oral vaccines against cholera and diarrhea caused by enterotoxigenic E. coli. The strong immunogenicity of CT and CTB can to a large extent be explained by their ability to bind to receptors on the intestinal mucosal surface. This has promoted much recent interest in the use of CTB as an oral delivery carrier for other vaccine-relevant antigens. Oral administration of antigens coupled to CTB either chemically or genetically has in several systems been found to markedly potentiate both intestinal and extra-intestinal IgA immune responses against the CTB-coupled antigens and to elicit substantial circulating antibody responses. In contrast to CTB, CT also has strong adjuvant properties for stimulating mucosal IgA immune responses to unrelated, non-coupled antigens after oral co-immunization. This adjuvant activity appears to be closely linked to the A subunit-catalyzed ADP-ribosylating action of CT leading to enhanced cyclic AMP formation in the affected cells.

Publication Types:
- Review
- Review, tutorial

PMID: 7958476, UI: 95046935

affected cell, and efforts to eliminate the enterotoxic activity without losing adjuvanticity have so far not met with success.

Publication Types:
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PMID: 8203723, UI: 94263008

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Modulation of an allergic immune response via the mucosal route in a murine model of inhalative type-I allergy.

Wiedermann U, Jahn-Schmid B, Repa A, Kraft D, Ebner C

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A murine model of aerosol inhalation, leading to sensitization to birch pollen (BP) and its major allergen Bet v 1, was established in order to try to influence type-I allergic immune responses via the mucosal route. We previously demonstrated that simultaneous inhalation of BP and cholera toxin, a potent mucosal adjuvant, induced a Th1-like immune response to the allergen in naive mice and modulated allergic immune responses in sensitized mice. In contrast to cholera holotoxin, mucosal application of the cholera B subunit (CTB) conjugated to antigen has been shown to induce peripheral tolerance in certain models of Th1-based autoimmune diseases. In the present study we investigated the potential of such an antigen delivery system to suppress Th2-based, allergic immune responses. Mucosal administration of CTB/Bet v 1 conjugates prior to sensitization led to significantly increased allergen-specific IgE/IgG1 and IgG2a antibody levels and cytokine production (IL-5, IFN-gamma) in vitro. Thus, CTB coupled to Bet v 1 acted as an adjuvant rather than a tolerogen. On the other hand we noted that mucosal application of CTB coupled to ovalbumin led to marked suppression of antigen-specific IgE antibody levels and IL-5 production in vitro and thereby restricted allergic sensitization. These results indicated that the effects of CTB/antigen conjugates depended on the nature of the antigen. In contrast to Bet v 1 coupled to CTB, nasal as well as oral application of low doses of unconjugated, Bet v 1 prior to aerosol sensitization inhibited allergen-specific antibody responses of all isotypes, cutaneous type-I skin tests in vivo as well as allergen-specific lymphoproliferative responses and cytokine production (IL-4, IL-5, IL-10, IFN-gamma) in vitro, suggesting that both T- and B-cell tolerance to the allergen were induced. Taken together, mucosal tolerance induction as well as the use of certain transmucosal antigen delivery systems might be promising new strategies to modulate type-I allergic immune responses

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1: *Int Immunol* 1999 Jul;11(7):1131-8

Corrected and republished in Int Immunol 1999 Oct;11(10):1717-24

Suppressive versus stimulatory effects of allergen/cholera toxoid (CTB) conjugates depending on the nature of the allergen in a murine model of type I allergy.

Wiedermann U, Jahn-Schmid B, Lindblad M, Rask C, Holmgren J, Kraft D, Ebner C

Division of Immunopathology, Institute of General and Experimental Pathology, University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria.

Recent reports have demonstrated that feeding small amounts of antigen conjugated to the B subunit of cholera toxin (CTB) suppress immune responses in experimental models of certain Th1-based autoimmune diseases. We have established a model of aerosol sensitization leading to Th2-mediated allergic immune responses in BALB/c mice. In the present study two different antigens, the dietary antigen ovalbumin (OVA) and the inhalant allergen Bet v 1 (the major birch pollen allergen), chemically coupled to recombinant CTB were tested for their potential to influence Th2-like immune responses. Intranasal administration of OVA-CTB prior to sensitization with OVA led to a significant decrease of antigen-specific IgE antibody levels, but a marked increase of OVA-specific IgG2a antibodies as compared to non-pretreated, sensitized animals. Antigen-specific lympho-proliferative responses in vitro were reduced by 65% in the pretreated group; IL-5 and IL-4, but not IFN-gamma, production were markedly decreased in responder cells of lungs and spleens of nasally pretreated mice. In contrast, mucosal administration of rBet v 1-CTB conjugates prior to sensitization led to an up-regulation of allergen-specific IgE, IgG1 and IgG2a, increased in vitro lympho-proliferative responses as well as augmented production of IL-5, IL-4, IL-10 and IFN-gamma. Intranasal administration prior to sensitization of unconjugated allergens showed also contrasting effects: OVA could not significantly influence antigen-specific antibody or cytokine production, whereas intranasal pretreatment with unconjugated Bet v 1 suppressed allergen-specific immune responses in vivo and in vitro. These results demonstrated that the two

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Strategies for the induction of immune responses at mucosal surfaces making use of cholera toxin B subunit as immunogen, carrier, and adjuvant.

Holmgren J, Czerkinsky C, Lycke N, Svennerholm AM

Department of Medical Microbiology and Immunology, University of Goteborg, Sweden.

The concept of a common mucosal immune system, through which specific antigen-activated lymphocytes from the gut can disseminate immunity both along the intestinal tract and to various other mucosal and glandular tissues, has generated much current interest in the possibility of developing oral vaccines, not only for enteric infections but also for infections in the respiratory and urogenital tracts. However, to date it has proven difficult in practice to stimulate strong mucosal IgA immune responses by either parenteral or oral-mucosal administration of most antigens, and experience with soluble protein antigens has, on the whole, been disappointing. A notable exception in this regard is cholera toxin (CT) and in humans more than in other species, its nontoxic B subunit pentamer moiety (CTB). Based on this, CTB has become an important component in recently developed oral vaccines against cholera as well as against diarrhea caused by enterotoxigenic Escherichia coli producing CT-like heat-labile enterotoxin(s). Since the strong immunogenicity of CT and CTB can, to a large extent, be explained by their ability to bind to receptors on the intestinal mucosal surface, there has recently been much interest in approaches using CTB as an oral delivery carrier system for other vaccine-relevant antigens, and much progress has been made in preparing immunogenic hybrid proteins by coupling various protein or peptide antigens chemically or genetically to CTB. Indeed, in several systems, oral administration of such hybrid antigens has been found to markedly potentiate both intestinal and extraintestinal IgA immune responses against the CTB-coupled antigens and also to elicit substantial circulating antibody responses. Besides the mucosal immunopotentiating effect of either CT or CTB owing to their similar capacity as oral antigen-delivery vehicles, CT, but in most systems tested not CTB, also has strong adjuvant properties for stimulating mucosal IgA immune responses to admixed (not coupled) unrelated antigens after oral immunization. This adjuvant activity appears to be closely linked to the ADP-ribosylating action of CT (and specifically of its A subunit) leading to enhanced cyclic AMP formation in the

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Role of GM1 binding in the mucosal immunogenicity and adjuvant activity of the Escherichia coli heat-labile enterotoxin and its B subunit.

de Haan L, Verweij WR, Feil IK, Holtrop M, Hol WG, Agsteribbe E, Wilschut J

Department of Physiological Chemistry, Groningen Utrecht Institute for Drug Exploration (GUIDE), University of Groningen, The Netherlands.

Escherichia coli (E. coli) heat-labile toxin (LT) is a potent mucosal immunogen and immunoadjuvant towards co-administered antigens. LT is composed of one copy of the A subunit, which has ADP-ribosylation activity, and a homopentamer of B subunits, which has affinity for the toxin receptor, the ganglioside GM1. Both the ADP-ribosylation activity of LTA and GM1 binding of LTB have been proposed to be involved in immune stimulation. We investigated the roles of these activities in the immunogenicity of recombinant LT or LTB upon intranasal immunization of mice using LT/LTB mutants, lacking either ADP-ribosylation activity, GM1-binding affinity, or both. Likewise, the adjuvant properties of these LT/LTB variants towards influenza virus subunit antigen were investigated. With respect to the immunogenicity of LT and LTB, we found that GM1-binding activity is essential for effective induction of anti-LTB antibodies. On the other hand, an LT mutant lacking ADP-ribosylation activity retained the immunogenic properties of the native toxin, indicating that ADP ribosylation is not critically involved. Whereas adjuvanticity of LTB was found to be directly related to GM1-binding activity, adjuvanticity of LT was found to be independent of GM1-binding affinity. Moreover, a mutant lacking both GM1-binding and ADP-ribosylation activity, also retained adjuvanticity. These results demonstrate that neither ADP-ribosylation activity nor GM1 binding are essential for adjuvanticity of LT, and suggest an ADP-ribosylation-independent adjuvant effect of the A subunit.

PMID: 9767427, UI: 98444394

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IgA isotype restriction in the mucosal but not in the extramucosal immune response after oral immunizations with cholera toxin or cholera B subunit.

Lycke N, Lindholm L, Holmgren J

Intestinal mucosal as well as extramucosal antibody responses were studied in mice after peroral immunizations with cholera toxin or cholera B subunit. The immunizations with cholera toxin gave rise to a marked response with antitoxin-secreting cells (PFC) in Peyer's patches (PP), mesenteric lymph nodes (MLN) and spleen showing isotype distribution of IgG greater than IgA greater than IgM and with PFC kinetics in MLN and spleen that suggested migration of cells from PP after peroral administration rather than cells stimulated in situ by adsorbed antigen. Highest numbers of PFC were obtained after 2 immunizations, and further administrations resulted in a decrease in the PFC response in MLN and spleen, while the PP responsiveness was relatively unchanged, and interestingly, protective immunity and IgA-dominated antitoxin titers in intestinal washings increased markedly by the additional boosters. Animals immunized with cholera B subunit, which lacks the adenylate cyclase-stimulating capacity of cholera toxin, showed similar PFC responses in extramucosal organs as those receiving cholera toxin but were poorly protected and had correspondingly lower IgA antitoxin titers in intestinal washings. These results suggest that the mucosal IgA antitoxin predominance is mainly due to regulatory mechanisms operating on the end-stage differentiation of the committed B cells in lamina propria and that this differentiation, as judged from the different results with cholera toxin and its B subunit, might be influenced by cyclic AMP.

PMID: 6874106, UI: 83264489

1: *Vaccine* 1998 Jan-Feb;16(2-3):286-92 Related Articles, Books, LinkOut

Induction of mucosal and systemic immune responses by intranasal immunization using recombinant cholera toxin B subunit as an adjuvant.

Wu HY, Russell MW

Department of Microbiology, University of Alabama at Birmingham 35294-2170, USA. medm115@uabdpo.dpo.uab.edu

Intranasal (i.n.) immunization with Streptococcus mutans surface protein AgI/II mixed with cholera toxin B subunit (CTB) containing a trace amount of cholera toxin (CT) induces strong immune responses in mucosal and systemic sites, but whether pure CTB alone has an adjuvant effect has been questioned. To determine the adjuvant effect of recombinant (r) CTB, mice were immunized with 10 micrograms of AgI/II either mixed with or conjugated to 5 micrograms of rCTB, and antibody responses in saliva, nasal wash, gut wash, vaginal wash, and serum were assayed by ELISA. The results showed that AgI/II either mixed with or conjugated to rCTB could induce both mucosal IgA and systemic IgG antibodies to higher levels than in mice similarly immunized with AgI/II alone. Some responses, especially serum IgG antibodies, were enhanced by adding 5 micrograms CT to the immunogen, whereas overall mice immunized with AgI/II mixed with CTB contaminated with CT tended to generate the strongest mucosal IgA and serum IgG responses to AgI/II. However, rCTB used as an adjuvant induced lower antibody responses against itself than CTB intentionally or inadvertently mixed with CT. These results show that rCTB can serve as an adjuvant for protein immunogens administered by the i.n. route.

PMID: 9607044, UI: 98269927

Intranasal sensitization of Japanese cedar pollen by the co-administration of low doses of cholera toxin but not its recombinant B subunit to mice.

Hirai T, Hashiguchi S, Torigoe N, Toda Y, Ito Y, Sugimur K

Department of Bioengineering, Faculty of Engineering, Kagoshima University, Kagoshima, Japan.

We evaluated the effects of cholera toxin (CT) and the B subunit of cholera toxin (CTB) on the intranasal sensitization of Japanese cedar pollen (JCP) in mice. JCP suspended in phosphate-buffered saline was administered into the nostrils of mice in combination with varying doses of CT or recombinant CTB(r-CTB) once a week for 5 weeks. Antibody responses specific to sugi basic protein (SBP) were monitored by ELISA for seven weeks. The sensitization of JCP alone did not induce IgG1, IgG2b, IgG2a, IgE or IgA. In contrast, sensitization of JCP in combination with CT (JCP/CT) elicited the prominent production of SBP-specific IgG1 and low levels of IgG2b and IgG2a on Day 49. IgE production was detected only in the serum of mice which were treated with JCP/CT, and not under any other protocol. Using spleen cells from these mice, cytokine production was examined by ELISA in culture supernatants after they had been stimulated in vitro with major cedar pollen allergens, Cry j 1, Cry j 2 or SBP. Notable responses were an increase of IFN-gamma as well as IL-4 in JCP/CT-sensitized cells stimulated with Cry j 2, but not in those stimulated with Cry j 1. No significant differences were detected in IL-5 production among the experimental groups. Histopathological examination, however, showed that eosinophil infiltration was evident in the nasal mucosa of the JCP/CT-sensitized mice following challenge with JCP/CT, but weak with BSA/CT or CT alone. Thus, the immunological and histological analyses indicated that the co-administration of a low dose of CT in combination with JCP allows the induction of pollen-allergic states in mice.

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Comparison of systemic and mucosal priming for mucosal immune responses to a bacterial protein antigen given with or coupled to cholera toxin (CT) B subunit, and effects of pre-existing anti-CT immunity.

Wu HY, Russell MW

Department of Microbiology, University of Alabama at Birmingham 35294.

Intraperitoneal immunization with a bacterial protein antigen conjugated to cholera toxin B subunit (CTB) was generally less effective than intragastric or intranasal immunization in generating mucosal IgA antibodies, and in priming the mucosal immune system to respond to intragastric or intranasal boosting. Previous intragastric or intranasal immunization which generated high levels of mucosal and circulating antibodies to CTB did not suppress mucosal IgA responses induced by intragastric or intranasal immunization with bacterial antigen conjugated to or mixed with CTB, but serum antibody responses were inhibited depending on the route of immunization and whether CTB was conjugated to or mixed with the antigen.

PMID: 8165853, UI: 94219163

1: *Proc Natl Acad Sci U S A* 1994 Nov 8;91(23):10795-9

Cholera toxin B subunit: an efficient transmucosal carrier-delivery system for induction of peripheral immunological tolerance.

Sun JB, Holmgren J, Czerkinsky C

Department of Medical Microbiology and Immunology, University of Goteborg, Sweden.

Oral administration of antigens, including allergens and autoantigens, may be an efficient way to prevent diseases associated with untoward immune responses to self- and non-self-antigens. However, this approach has met with limitations because it usually requires repeated administrations of large doses of antigen and is less efficient in an already immune host, and the effect is of short duration. We report that a single oral administration of minute amounts of particulate or soluble antigen coupled to the B subunit of cholera toxin (CTB) can markedly suppress systemic immune responses in naive and in systemically immune animals. Both early (2-4 hr) and late (24-48 hr) delayed type-hypersensitivity reactivities were strongly suppressed after feeding a single dose of CTB-conjugated antigen. Serum antibody responses were also decreased, although moderately, after oral administration of CTB-conjugated antigen. This strategy of tolerance induction, based on oral administration of small amounts of antigens conjugated to a mucosa-binding molecule, may find broad applications for preventing or abrogating untoward immune responses.

Comments:

- Comment in: Proc Natl Acad Sci U S A 1994 Nov 8;91(23):10762-5

PMID: 7526379, UI: 95062151

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[Immunological mechanisms in allergen-specific immunotherapy: impact on future trends in type-1 allergy management].

[Article in German]

Ebner C

Institut fur Allgemeine und Experimentelle Pathologie, Wien.

Specific immunotherapy (SIT) is the only treatment of Type-I allergy that leads to a modulation of the immune response to the eliciting allergen. The repeated administration of high doses of antigen induces a state of "antigen-specific non-responsiveness", i.e. immunologic tolerance to the injected antigen. Accordingly, during and after SIT the proliferative response of allergen-specific T lymphocytes in response to the administered antigen are significantly reduced. According to recent publications, this effect is due to the production of the immunosuppressive cytokine interleukin (IL)-10, which is induced during the treatment. On the other hand, a distinct change in the quality of the immune response to the injected allergen can be observed: the production of the IgE-inducing cytokine IL-4 by T helper cells decreases. Moreover, the release of other proinflammatory cytokines and inflammatory mediators is suppressed. Together, these events result in a marked decrease of symptoms during allergen exposure and reduced reactivity during challenge.

Publication Types:
- Review
- Review, tutorial

PMID: 10584289, UI: 20051678

Corrected and republished article originally printed in Int Immunol 1999 Jul;11(7):1131-8

Suppressive versus stimulatory effects of allergen/cholera toxoid (CTB) conjugates depending on the nature of the allergen in a murine model of type I allergy.

Wiedermann U, Jahn-Schmid B, Lindblad M, Rask C, Holmgren J, Kraft D, Ebner C

Division of Immunopathology, Institute of General and Experimental Pathology, University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria.

Recent reports have demonstrated that feeding small amounts of antigen conjugated to the B subunit of cholera toxin (CTB) suppress immune responses in experimental models of certain T(h)1-based autoimmune diseases. We have established a model of aerosol sensitization leading to T(h)2-mediated allergic immune responses in BALB/c mice. In the present study two different antigens, the dietary antigen ovalbumin (OVA) and the inhalant allergen Bet v 1 (the major birch pollen allergen), chemically coupled to recombinant CTB were tested for their potential to influence T(h)2-like immune responses. Intranasal administration of OVA-CTB prior to sensitization with OVA led to a significant decrease of antigen-specific IgE antibody levels, but a marked increase of OVA-specific IgG2a antibodies as compared to non-pretreated, sensitized animals. Antigen-specific lympho-proliferative responses in vitro were reduced by 65% in the pretreated group; IL-5 and IL-4 production were decreased in responder cells of lungs and spleens of nasally pretreated mice. In contrast, mucosal administration of rBet v 1-CTB conjugates prior to sensitization led to an up-regulation of allergen-specific IgE, IgG1 and IgG2a, increased in vitro lympho-proliferative responses as well as augmented production of IL-5, IL-4, IL-10 and IFN-gamma. Intranasal administration prior to sensitization of unconjugated allergens showed also contrasting effects: OVA could not significantly influence antigen-specific antibody or cytokine production, whereas intranasal pretreatment with unconjugated Bet v 1 suppressed allergen-specific immune responses in vivo and in vitro. These results

demonstrated that the two antigens-in conjugated as in unconjugated form-had different effects on the T(h)2 immune responses. We therefore conclude that the tolerogenic or immunogenic properties of CTB-and probably also other antigen-delivery systems-strongly depend on the nature of the coupled antigen-allergen.

Publication Types:

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PMID: 10508191, UI: 99437895

antigens--in conjugated as in unconjugated form--had different effects on the Th2 immune responses. We therefore conclude that the tolerogenic or immunogenic properties of CTB--and probably also other antigen-delivery systems--strongly depend on the nature of the coupled antigen-allergen.

PMID: 10383946, UI: 99315317

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Cholera toxin B subunit as a carrier protein to stimulate a mucosal immune response.

McKenzie SJ, Halsey JF

Horseradish peroxidase (HRP) was covalently coupled to the binding subunit of cholera toxin (CTB) via a two-step glutaraldehyde procedure. The HRP-CTB conjugate was characterized by physiochemical as well as immunochemical methods. Mice were immunized intraduodenally with the HRP-CTB conjugate, with HRP alone, or with a mixture of uncoupled CTB and HRP. The functionally active dose of CTB was 50 micrograms and the HRP dose was in the 30- to 90-micrograms range. Both IgA and IgG antibody responses were measured in serum, intestinal washes, and bile by using a solid phase immunoradiometric assay. Mice immunized with the HRP-CTB conjugate showed a significantly higher level of IgA anti-HRP in intestinal washes and bile, as well as increased levels of serum IgG anti-HRP. Animals that received only HRP or the mixture of CTB and HRP had reduced levels of HRP-specific antibody of either class in both gut washes and bile. The IgA anti-HRP responses in the gut washes were 33- to 120-fold higher when the conjugate was used as the immunogen in comparison with immunization with the CTB + HRP or the HRP alone. Vaccines to stimulate mucosal immunity to any antigenic determinant might thus be prepared by covalent conjugation to effective mucosal immunogens such as CTB.

PMID: 6470484, UI: 84290652